**What role does dopamine really play in tobacco addiction?**

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*A prevailing narrative explaining tobacco addiction is that uptake of nicotine in the brain causes dopamine release in the nucleus accumbens which rewards the behaviour that led to it. However, evidence suggests that in this and other addictive disorders a more nuanced, multi-level model is required that recognises how dopamine interacts with other parts of a complex system to maintain maladaptive behaviour patterns.*

The role of mesocortical-mesolimbic dopaminergic pathway in drug addiction has been extensively investigated in the last 30 years [1]. Many but not all [see 1] addictive drugs have been shown to induce activation of this pathway either at the level of dopaminergic cell firing or increased dopamine concentrations in target brain areas such as nucleus accumbens. Thus, the 'dopaminergic signal' has been considered as a key mechanism underlying abuse potential, drug self-administration, addiction development and maintenance [2]. Tobacco addiction is considered by many to be a *dopaminergic accumbal self-administration* disorder with nicotine as the primary pharmacological agent.

For tobacco addiction the simple version of this narrative is undermined by the relative weakness of nicotine as a behavioural reinforcer in animal models and the low efficacy of nicotine replacement therapy (NRT) as an aid to smoking cessation – even under optimal conditions some 80% of smokers using NRT in a quit attempt resume smoking [3]. In addition, after the first one or two cigarettes of the day, key nicotinic receptors are in a desensitised state so further tobacco use does not appear to trigger dopaminergic activity in the neural pathway believed to lie at the heart of the process [4].

The simple version of the dopamine hypothesis of tobacco addiction is further weakened by the fact that bupropion and nortriptyline have similar efficacy to nicotine replacement therapies as smoking cessation aids despite having at best weak activity on dopaminergic pathways [5, 6, 7, 8]. Crucially, after decades of research not a single drug with a full and selective dopaminergic mechanism of action has been found to help with smoking cessation or recovery from any addictive disorder [9].

More recently, the advent of electronic cigarettes is leading to a reconsideration of the nicotine-dopamine narrative in tobacco use. Modern e-cigarettes can provide smokers with as much nicotine as they were receiving from their conventional cigarettes, ingested with roughly equal rapidity [10]. However, in countries such as the UK where they are readily available and millions of smokers have used them in an attempt to quit smoking, the effectiveness to date is broadly similar overall to NRT [11]. At the same time, a substantial minority of smokers and ex-smokers choose to use e-cigarettes that do not contain nicotine but do contain flavourings or various kinds [12].

Critiques of the dopaminergic narrative in nicotine dependence are not new. In 2003 [13], John Dani described ‘wrinkles’ in the dopamine hypothesis. He pointed out that dopamine release is associated with nicotine self-administration but is not necessary for behavioural demonstration of nicotine reward. Moreover, while dopamine antagonism reduces the behavioural reward from nicotine, nicotine self-administration can occurs at high doses that are aversive.

Part of the problem lies in the misconception of a one-to-one correspondence between dopamine transmission in the nucleus accumbens and behavioural reward. More likely, dopamine transmission signals unpredicted and novel information from the environment, and participates in an update of environmental saliency for both rewarding and aversive stimuli, and its integration into adaptive, motivated behaviours [14].

A further potential complication arises from evidence in animal models that nicotine may somehow act as a 'reward amplifier': increasing the reward value of other stimuli such as food or pleasant flavours [15, 16]. This is separate from the potential role of secondary reinforcers (stimuli associated with nicotine uptake) in promoting and tobacco use [17]. The idea is that a mildly rewarding stimulus such as the aroma of tobacco may become more rewarding if nicotine is present in the CNS. While this hypothesis must be considered very preliminary as a basis for tobacco addiction, it highlights the potentially complex interactions that may arise between pharmacological and non-pharmacological drivers of behaviour.

Critiques of the simple version of the dopamine hypothesis as a cornerstone of addiction theory apply to other addictions as well as tobacco [1, 18]. Part of the argument involves reference to other neuropharmacological mechanisms that have been found to be important that appear to have little or nothing to do with dopamine [18]. Another, part is the recognition that social and psychological factors have a huge role to play in uptake, development and maintenance of addictive behaviours [19].

Accommodating all the available evidence in a single systems model will be challenging but ought to be a key objective in the field [11]. Such a model will need to recognise the role of dopamine in tobacco addiction under a broader and more evolutionary conceptualization; the dopamine signal is the mediator not only of pleasure and reward, but also of aversion, novelty, expectation, prediction errors, decision-making, and in general of the information processing from/to tobacco user's environment. The roles of gender, age, genetic factors and comorbidities that have been identified

as important in initiation, maintenance and relapse need to be brought into the model and integrated with neurobiological explanations.

Research is needed into the biobehavioural mechanisms underlying the full range of factors that influence development of, and relapse to, tobacco addiction. This 'reverse translation' approach may help not only to understand how these factors influence outcomes but also to identify novel targets for pharmacological and psychological interventions.

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